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A REVIEW ON RECENT TRENDS IN NIOSOMAL ANTIGLAUCOMA DRUG DELIVERY SYSTEM

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ABSTRACT

The chronic glaucoma with open angle is the second leading cause of blindness in the world. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. Poor bioavailability of drugs from ocular dosage form is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium. Conventional preparations require frequent instillation, and long term use of such preparations and can cause ocular surface disorders. In recent years, significant efforts have been directed towards the development of new carrier systems for ocular drug delivery. Among these, non-ionic surfactant vesicles *i.e.* niosomes could be a potential one for the effective treatment of glaucoma patients and have gained popularity in ocular drug delivery research. This article reviews the constraints of conventional ocular therapy, complications of glaucoma therapy, and newer advances in the field of anti-glaucomatic niosomal formulation.

Keywords: Niosomes, Glaucoma, Ocular delivery.

INTRODUCTION

The eye is one of the most delicate and yet most valuable of the sense organs and is a challenging subject for topical administration of drugs to the eye. The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges[1].

Because many parts of the eye are relatively inaccessible to systemically administered drugs, the drugs may require delivery to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intra-ocular treatment *via* the cornea for diseases such as glaucoma and uveitis[2,3]. The most convenient way of delivering drugs to the eye is in the form of eye drops. But the preparation when instilled into the cul-de-sac is rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage[4]. Only a small amount is available for its therapeutic effect resulting in frequent dosing[5,6]. Cul-de-sac of the eye normally holds 7 µl of tear. But the volume of drops is approximately 40-50 µl. This also leads to rapid tear secretion deviating from its normal flow rate of 1 µl/min, and causes subsequent drainage of eye drops. Due to the resulting elimination rate, the precorneal half life of drugs following application of these pharmaceutical formulations is considered to be between about 1-3 min. As a consequence, only the very small amount of about l-3% of the drug actually penetrates through the cornea and is able to reach intraocular tissues[7]. In addition, the ocular residence time of conventional eye drops is limited to a few minutes due to lacrimation and blinking[8]; and the ocular absorption of a topically applied drug is reduced to approximately l-10%[9]. The drug is mainly absorbed systemically *via* conjunctiva and nasal mucosa[10], which may result in some undesirable side effects[11].

To overcome these problems, different approaches such as *in situ* forming[12,13], micro- and nanocarrier systems[14, 15], Inserts[16], and vesicular systems[17] have been adopted. In recent years, vesicles have become the vehicle of choice in ocular drug delivery. Vesicular systems not only help in providing prolonged and controlled action at the corneal surface but also help in providing controlled ocular delivery by preventing the metabolism of the drug from the enzymes present at the tear/corneal epithelial surface[13]. Moreover, vesicles offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that has the convenience of a drop, but will localize and maintain drug activity at its site of action[13]. Nonionic surfactant vesicles (niosomes) are promising drug carriers as they possess greater stability and lack of many disadvantages associated with phospholipid vesicles (liposomes), such as high cost, stringent storage condition and the oxidative degradation of phospholipids[18]. Glaucoma is a disease with a characteristic of higher level of intraocular pressure (IOP) which might progressively hurt visibility. The average IOP of population is 15.5 ± 2.57 mmHg. If people whose IOP is 20.5 mmHg or higher could be suspected of having glaucoma and IOP over 24 mmHg is a definite case of glaucoma[19]. The chronic glaucoma with open angle poses a major problem of public health and it is the second leading cause of blindness in the world[20]. Its

treatment requires a long and prolonged therapy and thus, niosomes could be a useful vesicular system for the treatment of glaucoma. The present review highlights various complications of glaucoma therapy with mostly available and/or newer drugs, novel strategies in the development of anti-glaucomatic niosomal systems and the challenges standing ahead.

CHALLENGES IN GLAUCOMA THERAPY

Many ongoing clinical studies are trying to find neuroprotective agents (memantine, glatiramer acetate) that might benefit the optic nerve and certain retinal cells in glaucoma. The treatment of open angle glaucoma and secondary glaucoma is primarily with drugs, whereas the narrow-angle or congenital types is primarily surgical. Long-term use of ocular drugs, as in glaucoma patients who are treated for decades after they are diagnosed, frequently causes tear film and conjunctival involvement, sometimes resulting in sight threatening ocular surface disorders[21.25]. Moreover, higher concentration of some drugs causes allergy at the ocular surface such as α2-agonist brimonidine shows concentration dependent allergy due to oxidation of the drug[26]. Prolonged use of eye medications with preservatives presents a certain risk to ocular surface, such as thickness of sub-epithelial collagen of conjunctiva[27], a chronic sub-clinical inflammation as shown by the presence of immunologic changes and inflammatory infiltrates[28]. Medications placed in the eye are absorbed into the conjunctival blood vessels on the eye surface. A certain percentage of the active ingredient of the medication, though small, will enter the blood stream and may adversely affect functions such as heart rate and breathing. Hence, there is a need to develop an alternative ophthalmic preparation and in this context, niosomal preparations may be the alternative.

FORMULATION CONSIDERATIONS

Niosomes are formed by self-assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in non-aqueous solvent[29].

Surfactants

Van Abbe30 explained that the non-inonic surfactants are preferred because the irritation power of surfactants decreases in the following order: cationic> anionic> ampholytic>

non-ionic. The ether type surfactants with single alkyl chain as hydrophobic tail, is more toxic than corresponding dialkylether chain. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter because ester-linked surfactant is degraded by esterase to triglycerides and fatty acid *in vivo*[31]. The surfactants with alkyl chain length from C12-C18 are suitable for the preparation of niosomes[32]. Span series surfactants having hydrophilic lipophilic balance (HLB) number of between 4-8 can form vesicles[33]. Guinedi et al.[34] prepared niosomes from Span 60 and Span 40 to encapsulate acetazolamide (ACZ). Highest drug entrapment efficiency was obtained with Span 60 in a molar ratio of 7:6 with cholesterol. They found that both the surfactants were nonirritant with ocular tissues however; only reversible irritation of substantia propia was observed in the rabbit eye.

Charge inducer

Charge inducer is used to impart charge on the vesicles to increase its stability by preventing fusion of vesicles and providing higher value of zeta potential. The commonly used positively charge inducers are stearylamine, cetyl pyridinium chloride and negatively charge inducers are lipoamino acid and dicetyl phosphate. Aggarwal and his coworkers[35] formulated niosomes by reverse phase evaporation method to encapsulate ACZ using Span 60, cholesterol, positively (stearyl amine), and negatively (dicetyl phosphate) charge inducers. Drug entrapment efficiency varied with the charge and the percent entrapment efficiency was found to be 43.75%, 51.23% and 36.26% for neutral, positively charged and negatively charged niosomes, respectively. The positively charged niosomes, although showed good corneal permeability and IOP lowering capacity, were however seemed to be inappropriate in terms of the corneal cell toxicity.

Bioadhesive polymer

Bioadhesive polymers are the other membrane additives that are used to provide some additional properties to the niosomes. Carbopol 934P-coated niosomal formulation of ACZ, prepared from Span 60, cholesterol, stearylamine or dicetyl phosphate exhibited more tendency for the reduction of intraocular pressure compared to that of a marketed formulation (Dorzox)[35]. Aggarwal and Kaur[36] prepared chitosan and carbopol-coated niosomes to entrap antiglaucoma agent timolol maleate by reverse phase evaporation method. Polymer coating

extended the drug release up to 10 h (releasing only 40-43% drug). However, in comparison, chitosan coated niosomes showed a better sustained effect.

Steric Barrier

Some researchers[37] examined the aggregation behavior of monomethoxypoly (ethylene glycol) cholesteryl carbonates in mixture with diglycerol hexadecyl ether and cholesterol. They obtained non-aggregated, stable, unilamellar vesicles at low polymer levels with optimal shape and size homogeneity at cholesteryl conjugate/lipids ratios of 5-10 mol%. Higher levels up to 30 mol% led to the complete solubilization of the vesicles into disk-like structures of decreasing size with increasing polyethylene glycol content. This study revealed the bivalent role of the derivatives; while behaving as solubilizing surfactants, they provided an additional efficient steric barrier, preventing the vesicles from aggregation and fusion over a period of at least 2 weeks.

Isotonic stabilizer

Development of a topically effective formulation of ACZ is difficult because of its unfavorable partition coefficient, solubility, permeability coefficient, and poor stability at the pH of its maximum solubility. Based on these factors and the ability of niosomes to come into complete contact with corneal and conjunctival surfaces, niosomal drug delivery system has been investigated to enhance the corneal absorption of ACZ. Boric acid solution (2%) is isotonic with tears and could be used as a vehicle for the ACZ niosomal formulations because the pH of maximum stability for ACZ is 4.0. A recent study revealed that boric acid solution can maintain the pH between 4.0 and 5.0. In addition, the pharmacodynamic studies showed more than 30% fall in IOP which was sustained up to 5 h[38].

Methods of preparation

This affects mainly the vesicle lamellarity, entrapment efficiency, and size. For example, reverse phase evaporation method produces large unilameller vesicles appropriate for higher entrapment of water soluble drugs. Film hydration method produces multilamellar niosomes which after sonication gives unilamellar niosomes. Recently, it has been reported that reverse phase evaporation method afforded the maximum drug entrapment efficiency (43.75%) as compared with ether injection (39.62%) and film hydration (31.43%) methods[35]. Vyas et al.[39] prepared discoidal vesicles (discome) by treating niosomes with solulan C24 (poly-24-

oxyethylene cholesteryl ether). Discosomes were of larger sizes (12-60 µm) and these entrapped higher quantity of timolol maleate. Their disc sizes provided better ocular localization. The discomes were found to be promising for controlled ocular administration of water soluble drugs.

Niosomes can be prepared by a number of methods which are as follows:

- Ether injection method: In this method, a solution of the surfactant is made by dissolving it in diethyl ether. This solution is then introduced using an injection (14 gauge needle) into warm water or aqueous media containing the drug maintained at 60°C. Vaporization of the ether leads to the formation of single layered vesicles. The particle size of the niosomes formed depend on the conditions used, and can range anywhere between 50-1000µm[40].
- Hand shaking method (Thin Film Hydration Technique): In this method a mixture of the vesicle forming agents such as the surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether or chloroform in a round bottom flask. The organic solvent is removed at room temperature using a rotary evaporator, which leaves a thin film of solid mixture deposited on the walls of the flask. This dried surfactant film can then be rehydrated with the aqueous phase, with gentle agitation to yield multilamellar niosomes. The multilamellar vesicles thus formed can further be processed to yield unilamellar niosomes or smaller niosomes using sonication, microfluidization or membrane extrusion techniques[40].
- Reverse phase evaporation technique: This method involves the creation of a solution of cholesterol and surfactant (1:1 ratio) in a mixture of ether and chloroform. An aqueous phase containing the drug to be loaded is added to this, and the resulting two phases are sonicated at 4-5°C. A clear gel is formed which is further sonicated after the addition of phosphate buffered saline (PBS). After this the temperature is raised to 40°C and pressure is reduced to remove the organic phase. This results in a viscous niosome suspension which can be diluted with PBS and heated on a water bath at 60°C for 10 mins to yield niosomes[41].
- Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote loading): In this method, a solution of surfactant and cholesterol is made in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask, similar to the hand shaking method. This film is then hydrated using citric acid solution (300mM, pH 4.0) by vortex mixing. The resulting multilamellar vesicles are then

treated to three freeze thaw cycles and sonicated. To the niosomal suspension, aqueous solution containing 10mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 using 1M disodium phosphate (this causes the drug which is outside the vesicle to become non-ionic and can then cross the niosomal membrane, and once inside it is again ionized thus not allowing it to exit the vesicle). The mixture is later heated at 60°C for 10 minutes to give niosomes[42].

- The "Bubble" Method: It is a technique which has only recently been developed and which allows the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks, and this is positioned in a water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck, while the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70°C. This dispersion is mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70°C using the nitrogen gas to yield niosomes[43].
- Formation of Proniosomes and Niosomes from Proniosomes: To create proniosomes, a water soluble carrier such as sorbitol is first coated with the surfactant. The coating is done by preparing a solution of the surfactant with cholesterol in a volatile organic solvent, which is sprayed onto the powder of sorbitol kept in a rotary evaporator. The evaporation of the organic solvent yields a thin coat on the sorbitol particles. The resulting coating is a dry formulation in which a water soluble particle is coated with a thin film of dry surfactant. This preparation is termed Proniosome[44].

CONCLUSION

In the last couple of years, continuous research have been going on for better delivery of anti-glaucoma drugs with the aim of more localized drug delivery, minimization of dosing frequency. An ophthalmic should preferably release drug at a controlled rate to prolong the effect in reducing IOP and should be nontoxic and comfortable for patient use. Niosomal system could afford such characteristics and could be a useful ocular delivery system for antiglaucoma drugs. World health organisation (WHO) World Health Bulletin 2002 declared that 12.30% of total blindness would be because of glaucoma. However, the situation will be worsening because large number of people will fall into the geriatric group. In these consequences, more research should be continued with niosomes for the effective glaucoma therapy.

FUTURE PERSPECTIVE

In future, much of the emphasis will be given to achieve noninvasive sustained drug release for eye disorders in both segments. A clear understanding of the complexities associated with tissues in normal and pathological conditions, physiological barriers, and multicompartmental pharmacokinetics would greatly hasten further development in the field.

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